PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference SPI0627WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2008/053372	International filing date *(day/month/year)* 20 March 2008 (20.03.2008)	Priority date *(day/month/year)* 23 March 2007 (23.03.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant UNIMED PHARMACEUTICALS, LLC		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 29 September 2009 (29.09.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Agnes Wittmann-Regis e-mail: pt06.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2008/053372	International filing date *(day/month/year)* 20.03.2008
Priority date *(day/month/year)* 23.03.2007	
International Patent Classification (IPC) or both national classification and IPC INV. A61K31/568 A61P15/08	
Applicant UNIMED PHARMACEUTICALS, INC	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Bonzano, Camilla Telephone No. +31 70 340-2202

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/053372

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	20
	No:	Claims	1-19
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	-

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V

1. Reference is made to the following documents:

D1: WO 2007/044976 A (UNIMED PHARMACEUTICALS INC [US]; MALLADI RAMANA [US]) 19 April 2007

D2: US 2004/072810 A1 (MASINI-ETEVE VALERIE [FR] ET AL) 15 April 2004

D3: WO 02/17926 A (UNIMED PHARMACEUTICALS INC [US]; LAB BESINS ISCOVESCO [US]) 7 March 2002 (2002-03-07)

D4: WO 2005/076899 A (UNIV WASHINGTON [US]; AMORY JOHN K [US]; BREMNER WILLIAM J [US]) 25 August 2005 (2005-08-25)

D5: WO 2004/037173 A (UNIMED PHARMACEUTICALS INC [US]) 6 May 2004

D6: RICHMOND E J ET AL: "Male pubertal development and the role of androgen therapy" NATURE CLINICAL PRACTICE ENDOCRINOLOGY AND METABOLISM 2007 UNITED KINGDOM, vol. 3, no. 4, 2007, pages 338-344, XP080822235

D7: ROGOL A D: "New facets of androgen replacement therapy during childhood and adolescence" EXPERT OPINION ON PHARMACOTHERAPY 2005 UNITED KINGDOM, vol. 6, no. 8, 2005, pages 1319-1336, XP008082228

D8: DROBAC S ET AL: "A Workshop on pubertal hormone replacement options in the United States" JOURNAL OF PEDIATRIC ENDOCRINOLOGY AND METABOLISM 2006 ISRAEL, vol. 19, no. 1, 2006, pages 55-64, XP008082229

D9: MATSUMOTO A M: "Hormonal therapy of male hypogonadism" ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA 1994 UNITED STATES, vol. 23, no. 4, 1994, pages 857-875, XP008082230

D10 ARISAKA O ET AL: "Systemic effects of transdermal testosterone for the treatment of microphallus in children." PEDIATRICS INTERNATIONAL OFFICIAL JOURNAL OF THE JAPAN PEDIATRIC SOCIETY APR 2001, vol. 43, no. 2, April 2001 (2001-04), pages 134-136, XP008082233

Unless otherwise specified, reference is made to the passages cited in the search report.

Novelty

2.1 D3 describes a method of treating hypogonadism in male subjects comprising applying a hydroalcoholic gel containing testosterone to the skin of said male subjects. A packet comprising 25 mg of testosterone is disclosed (claim 34) and a dispenser of the gel is disclosed in example 2.

D5 describes patients receiving 5.0 g/day of Androgen (delivering 50 mg/day of

testosterone to the skin of which about 10% or 5 mg is absorbed).
The subject-matter of claims 19,20 is not new over D3,D5.

2.2 Concerning the second medical use claims, the treatment of the same disease with the same compound represent a novel therapeutic application in view of the prior art, provided that two conditions are met:

(i) the treatment must be carried out on a novel group of subjects which is clearly distinguishable with respect to its physiological or pathological status from and does not overlap with the group previously treated.

(ii) the choice of the new group, if distinguishable from the known one, must not be arbitrary.

It seems here that these two conditions are met, and therefore the reference to "a adolescent boy" can be regarded as a feature capable of distinguishing the subject-matter of claim 1-18 from the closest prior art. This feature can therefore contribute to the novelty of the claimed subject-matter.

2.3 D4 discloses a testosterone replacement therapy (also in form of gel applied topically: see paragraph 7), that can be directed towards the adult as well as towards pubertal males of any age. Such individuals may be hypogonadal males (see paragraph 49), the same patients as in the present application.
The second medical use claims are therefore not novel in view of D4.
Concerning the composition claims, the attention of the applicant is drawn to the fact that claim for a package consisting of or comprising a product together with instructions for its use in a medical treatment amounts to a claim for a first medical use. Such a claim is not novel if it is not the first time that the product has been used in a medical treatment at that dosage.
The subject-matter of claims 1-19 is therefore not not new over D4.

2.4 D7 discloses the use of testosterone for topical administration in form of patch or hydroalcoholic gel for inducing pubertal development and for providing replacement therapy in boys with permanent hypogonadism. The patch is preferred, whereas the gel is said to be less commonly used: concerning the gel, a lower dose would be needed with respect to the formulation available in commerce, namely Androgel.
D8 discloses the use of testosterone for transdermal application (hydroalcoholic gel) for treating hypogonadal pubertal boys with delay of growth and pubertal development. Patches are more used: gels are also disclosed, but are said to be less preferred because

of the dosage available (not low enough) and because of lack of published experience in hypogonadal adolescents.
The subject-matter of claims 1-19 is therefore not not new over D7,D8.

2.5 The following documents are not novelty destroying.
D2 discloses the use of dihydrotestosterone (not testosterone) in the treatment of physiological conditions associated with insufficiency of DHT such as permanent hypogonadism, functional hypogonadism, hyperplasia of the prostate, gynaecomasty, micropenis in children. Micropenis is different from hypogonadism.
D9 describes the use of testosterone intramuscular for treating hypogonadism: in boys with secondary hypogonadism also other remedies are suggested.

Inventive step

3.1 Should the applicant overcome the above raised objections of lack of novelty, an inventive step has to be demonstrated, because the present subject matter, as far as novel, appears to be obvious in view of D4,D7,D8.
Hypogonadism is a disorders characterised in that the sex glands produce little or no hormones. In men, these glands (gonads) are the testes.
In boys, hypogonadism in childhood results in lack of muscle and beard development and growth problems. In men the usual complaints are sexual dysfunction, decreased beard and body hair, breast enlargement, and muscle loss.
It would be obvious for the man skilled in the art to expect from testosterone, already known for treating hypogonadism in adults and in pubertal males, and activity for treating hypogonadism in adolescent boys at the present dosages.

3.2 Moreover, the present subject matter seems obvious in view of D9 and D10.
D9 describes the use of intramuscular testosterone for treating hypogonadism: in boys with secondary hypogonadism also other remedies are suggested.
The present application differs from D9 in that the same compound is used on the same patients via topical instead of intramuscular application.
The problem to be solved is therefore to provide an alternative route of administration for treating hypogonadism in boys with testosterone.
Testosterone is well known for topical transdermal administration in form of hydroalcoholic gel: see D10 (transdermal testosterone for treating micropenis in boys)..
It would therefore be obvious for the man skilled in the art to expect also from a hydroalcoholic gel comprising testosterone an activity in treating hypogonadism in boys.

3.3 Finally it would be obvious to expect from transdermal testosterone, already known for treating hypogonadism in adults (D3,D5) also an activity in boys for treating the same disorder.
D3 describes a method of treating hypogonadism in male subjects comprising applying a hydroalcoholic gel containing testosterone to the skin of said male subjects. A packet comprising 25 mg of testosterone is disclosed (claim 34) and a dispenser of the gel is disclosed in example 2.
D5 describes patients receiving 5.0 g/day of Androgen (delivering 50 mg/day of testosterone to the skin of which about 10% or 5 mg is absorbed).
It would be obvious for the man skilled in the art to expect from testosterone, already known for treating hypogonadism in adults and in pubertal males, and activity for treating hypogonadism in adolescent boys when administered in the form of a hydroalcoholic gel, which is a well known form of administration of testosterone.

Other points

4. The attention of the Applicant is drawn to the fact that some documents are mentioned in the search report which might become relevant for novelty in some member states (see D1, indicated in the search report as a P document). The priority of the present application is valid: this document is therefore not relevant under the PCT.

4.1 D1 discloses a hydroalcoholic gel composition, useful for treating hypogonadism, comprising testosterone, isopropyl myristate, ethanol, water and thickening agent delivered topically in a dosage of 20-100 mg at a time also by a packet or a dispenser with a pump.

4.2 D6 is a literature article published after the valid priority date of the present application: it discloses the use of intramuscular testosterone in adolescents having hypogonadism. It is therefore too late.